

REMARKS

In the present application, claims 1-3 will remain pending in the instant application and stand ready for further action on the merits.

Claim Rejection under 35 U.S.C. § 103(a)

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Haneda et al.** US'480 (US 2002/0128480) in view of **Owa et al.** (Bioorganic and Medicinal Chemistry Letters 12 (2002) 2097-2100) and **Crassier et al.** WO'092 (WO 02/059092) further in view of <http://en.wikipedia.org/wiki/Tetrahydrofuran>.

Reconsideration and withdrawal of the instant rejection is respectfully requested based on the following considerations.

Legal Standard for Determining Prima Facie Obviousness

MPEP § 2141 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors are:

- (a) determining the scope and content of the prior art;
- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating any evidence of secondary considerations.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

Second, the Examiner has to provide some rationale for determining obviousness. MPEP § 2143 sets forth some rationales that were established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Exemplary rationales that may support a conclusion of obviousness include:

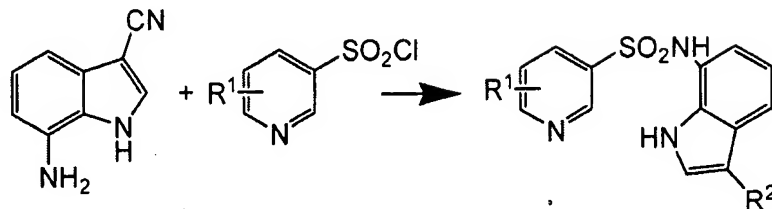
- (a) *combining prior art elements according to known methods to yield predictable results;*
- (b) *simple substitution of one known element for another to obtain predictable results;*
- (c) *use of known technique to improve similar devices (methods, or products) in the same way;*
- (d) *applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;*
- (e) *“obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success*
- (f) *known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;*
- (g) *some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.*

As the MPEP directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. See MPEP § 2143.03.

Distinctions Over the Cited Art

Owa et al.

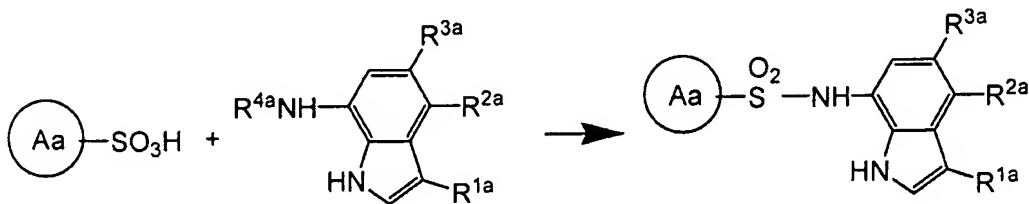
Owa et al. discloses the following reaction:



The solvent is ethyl acetate and the base is pyridine. However, **Owa et al.** never teaches or suggests that the above reaction can be carried out in a mixed solvent of water and C₁₋₆ alkyl acetate.

Haneda et al.

Haneda et al. discloses the following reaction (see paragraphs [0017]-[0019]):

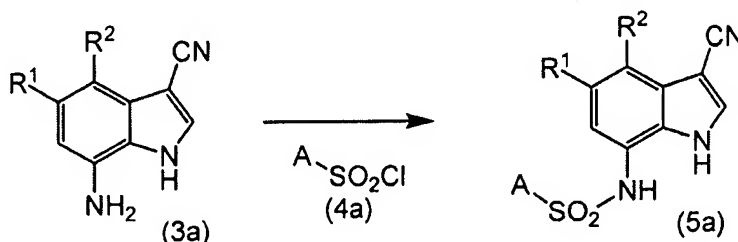


According to paragraph [0020], "Although there is no particular limitation for the solvent used for the reaction, those which dissolve the material substances and do not readily react with them are preferred. For example, pyridine, tetrahydrofuran, dioxane, benzene, ethyl ether, dichloromethane, dimethylformamide and a mixed solvent consisting of two or more which are selected from them can be used. In addition, when an acid is liberated with a progress of the reaction as in the case of using a sulfonyl halide in the reaction, it is preferred to conduct the reaction in the presence of an appropriate deacidifying agent and, therefore, the use of a basic

solvent such as pyridine is particularly appropriate. When a neutral solvent is used, a basic substance such as an alkali carbonate or an organic tertiary amine may be added. Of course, the solvent which can be used is not limited to those listed here."

The above reaction is carried out in THF in the presence of pyridine in Examples 1-7 and the above reaction is carried out in pyridine in Examples 9-10. Thus, **Haneda et al.** never teaches or suggests that the above reaction can be carried out in a mixed solvent of water and C₁₋₆ alkyl acetate.

On the other hand, the present invention uses a mixed solvent of water and C₁₋₆ alkyl acetate as the solvent for the following reaction:



As described in paragraph [0009] of the present specification, the advantages of using a mixed solvent of water and C₁₋₆ alkyl acetate are (1) safety of the concentration procedure is assured, (2) precipitation of the product is avoided, and (3) the total amount during extraction can be reduced since the reaction solvent also serves as the extraction solvent.

It was known in the art at the time of the priority date that THF tends to form peroxides. But, both of **Owa et al.** and **Haneda et al.** never teach or suggest water or a mixed solvent of water and an organic solvent; therefore those skilled in the art would never be motivated to use a mixed solvent of water and C₁₋₆ alkyl acetate to carry out the reaction in a solvent other than THF. Similarly, no reason or rationale is provided to those of ordinary skill in the art by **Owa et**

al. or **Haneda et al.** to use a mixed solvent of water and C₁₋₆ alkyl acetate to carry out the reaction in a solvent other than THF.

Reference Examples 1A to 4A in the present specification (*see paragraphs [0047] to [0063]*) correspond to the synthesis disclosed in **Haneda et al.** The present specification compares the method of the present invention with the method in **Haneda et al.** (*see paragraphs [0064] to [0070]*). As is clear from paragraphs [0067] to [0070], the present invention can carry out the reaction more efficiently than the method disclosed in **Haneda et al.**

Crassier et al.

Crassier et al. discloses that steps (1) to (3), i.e. formylation, conversion of formyl to oxime and cyanation, are carried out in a one-pot process and the one-pot process gives better yields compared with the stepwise synthesis. But this is not true. Examples 1.1 to 1.3 of **Crassier et al.** provide a stepwise synthesis of methyl 3-cyanoindole-7-carboxylate and Example 2.1 is a one-pot synthesis of the same compound. The yields of Examples 1.1 to 1.3 are 89.9% (*see page 19, line 6*), 95.0%^{*1} and 98.1%^{*2}, respectively.¹ The total yield of Examples 1.1 through 1.3 is 89.9% x 95.0% x 98.1% = 83.8%. On the other hand, the yield of Example 2.1 is 48.9% (*see page 21, line 16*). The yield by one-pot synthesis is remarkably lower than that by

¹ *1 and *2:

Molecular weights of methyl 3-formylindole-7-carboxylate (C₁₁H₉NO₃), methyl 3-(hydroxyiminomethyl)indole-7-carboxylate (C₁₁H₁₀N₂O₃) and methyl 3-cyanoindole-7-carboxylate (C₁₁H₈N₂O₂) are 203.20, 218.21 and 200.20, respectively.

The yield of Example 1.2 is $(5.1/218.21)/(5/203.20)*100 = 95.0\%$

The yield of Example 1.3 is $(4.5/200.20)/(5/218.21)*100 = 98.1\%$

stepwise synthesis. Those skilled in the art would never carry out one-pot synthesis in order to improve the yield. Crassier et al. actually teaches away from a one-pot synthesis.

For example, Crassier et al describes "The one-pot process gives better yields compared with the stepwise synthesis" (*see page 7, lines 7 - 8*). But this is merely stating the general principle that a one-pot synthesis generally gives better yields than a stepwise synthesis. But there are also synthesis reaction exceptions wherein a one-pot synthesis gives worse yields than a stepwise synthesis. As such, those skilled in the art would never know which method gives better yields without actually carrying out both syntheses (*i.e.*, one-pot and stepwise). In this respect, Crassier et al. is an exception case as shown by way of the above calculations. Again, the fact that Crassier et al. actually teaches away from a one-pot synthesis can be easily seen by comparing Examples 1.1 through 1.3 and Example 2.1 of Crassier.

Therefore, it is submitted that those skilled in the art would consider that formylation, conversion of formyl to oxime and cyanation in a one-pot process is not suitable in view of yields even though Crassier et al. may also describe the general principle "the one-pot process gives better yields compared with the stepwise synthesis."

In contrast, with regard to the instant invention, paragraphs [0064] to [0065] of the specification compare the yields of a stepwise synthesis and a one-pot synthesis of 3-cyano-4-methyl-7-nitro-1H-indole. The total yield of the stepwise synthesis is 85.8% and the yield of the one-pot synthesis is 97.6%. Thus the yield by the one-pot synthesis of the present invention is much higher than that by the stepwise synthesis of Haneda et al.

Based on such considerations, it is submitted that the cited art of record is incapable of providing those of ordinary skill in the art with any motivation, or reason or rationale for arriving

at the instant invention as claimed. Any contentions of the USPTO to the contrary must be reconsidered at present, as they are not sustainable.

CONCLUSION

Based upon the remarks presented herein, the Examiner is respectfully requested to issue a Notice of Allowance clearly indicating that each of the pending claims 1-3 is allowable under the provisions of Title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey, Reg. No. 32,881 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By 

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